Docket No.: MTI 3.0-025
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Govil et al.

Application No.: 08/883,075 Confirmation No.: 4799

Filed: June 26, 1997 Art Unit: 1617

For: ADHESIVE MIXTURE FOR TRANSDERMAL DELIVERY OF HIGHLY PLASTICIZING DRUGS Examiner: E. J. Webman

DECLARATION OF DR. GORDON FLYNN

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

I, Gordon L. Flynn, Ph.D., am a citizen of the United States, residing at 2115 Nature Cove Court, #202, Ann Arbor, MI 48104-4985.

1. I am an Emeritus Professor at the University of Michigan's College of Pharmacy. I have spent fully 39 years researching issues of mass transport of drugs into and through tissues such as the skin, especially including those aspects of formulations that enhance or promote delivery into and through the skin. From 1972 through 2001 I taught pharmacy students and pharmaceutical science graduate students about the skin and drug delivery into and through the skin. I've also taught them thermodynamics and both chemical and physical kinetics, the latter especially including issues of passive diffusion though membranes and matrices, particularly as those encountered in dermal and transdermal delivery. In the early

1990's I served the National Institutes of Health as a reviewer of grants involving drug delivery, especially including dermal and transdermal drug delivery, and in this capacity I was a permanent member of the Pharmacology Study Section for five years (I attended all but one session of the fifteen held over five continuous years). I've also served as a consultant to the United States Food and Drug Administration (FDA) on matters of dermal and transdermal delivery, on numerous occasions participating in AAPS/FDA sponsored workshops involving dermal and transdermal delivery. On multiple occasions I've given lectures dealing with topical and transdermal matters to FDA staff scientists. I presently serve as an advisor to the United States Pharmacopoeia and am particularly active in this capacity with respect to pharmacopoeial issues of topical and transdermal nature. I have authored or co-authored over 175 primary research articles, review articles and book chapters, the greater number of these articles dealing with fundamental issues of dermal and transdermal delivery. I have chaired the Gordon Research Conference on Barrier Function of Mammalian Skin and even had the attendees of a recent conference dedicate the conference to me as a salute upon my retirement (an unusual and highly complimentary gesture). I am a graduate of the Pharmacy School, Rutgers University, The State University of New Jersey (B.S. in Pharmacy in 1960) and of the University of Wisconsin School of Pharmacy (Ph.D. in Physical Pharmacy in 1965). While at Wisconsin I studied directly under Professor Takeru Higuchi, clearly the most brilliant physical scientist ever to practice in the pharmaceutical field.

2. I have familiarized myself with the above-identified, pending U.S. Patent Application No.

08/883,075, filed on June 26, 1997, in the name of Dr. Sharad K. Govil and Dr. Ludwig J. Weimann (hereinafter "the '075 application").

3. In that regard, I have also reviewed a copy of a rejection letter in that case dated October 26, 2004 in which claims 84, and 86-92 have been rejected on the basis of U.S. Patent No. 5,458,885 to Müller et al.

4. In particular, it is my understanding that the Examiner has taken the position that Müller *et al.* teaches a transdermal product which includes an acrylate base with polymers comprising a functionalizing monomer, C_4 to C_{12} acrylate and C_1 to C_4 acrylate. The Examiner has combined Müller *et al.* with U.S. Patent No. 4,861,800 to Buyske, which is said to teach diprenyl (selegiline) for treating Parkinson's disease, concluding that it would be obvious to add diprenyl to the composition of Müller *et al.*

5. I have very carefully read the full disclosure of Müller *et al.* This patent specifically refers to the fact that many medically active components contain one or more basic nitrogen atoms in the molecule, and can thus be used in transdermal compositions as either the free base or a salt form of the free base. Müller *et al.* notes that salt forms have higher water solubilities and are "more stable." It is stated therein, however, that for transdermal administration of such products, in most cases, the free base form,[1] although less suitable for storage purposes, is superior to the salt in terms of penetrating the lipophilic barrier of the human cornea (stratum corneum). The Müller *et al.* patent thus claims to have provided an adhesive polymer material which, as

[1] The free base is the non-ionic, alkaline form of the salt of a weak base. With two unshared electrons, it has the properties of a so-called Lewis base.

compared to the prior art, demonstrates improved component delivery for basic active components. This is said to be accomplished by Müller *et al.* by preparing a pressure-sensitive adhesive polymer that includes, in part, monomers that have a basic (amine) character. In particular, the basic (amine) component of the adhesive backbone is said to release the base form of the active component from salts of the active component for diffusion through the skin, the point being illustrated using bopindolol hydrogen malonate as the example salt. Müller *et al.* state that it is thus necessary to use monomers with corresponding basic groups which can, for example, comprises a list of amines which is set forth as column 4, lines 32 to 38 thereof. It is clear from the description of the invention that Müller *et al.* envision an exchange of the acid portion of the drug salt with the pendant amine functional groups on the formed polymer backbone, thereby freeing the base portion of the salt, the active drug, to diffuse through the adhesive up to and into and through the skin.

6. I also understand that claims 84 and 86-92 as currently presented in this application are each specifically directed to blends of a hydrophobic acrylic polymer which is used with a highly plasticizing drug, such as diprenyl (selegiline).

7. My analysis begins with an understanding that a hydrophobic substance is an apolar (non-polar) substance. This means that it cannot and does not interact with other molecules via hydrogen bonds and/or strong dipolar interactions arising from an internal charge separation (an

electrical dipole moment) in the molecule.[2] The thrust of the Müller *et al.* patent, however, in requiring the incorporation of amine functionalities in the polymerized adhesive, is to create polarity in the adhesive given that amine functionalities exhibit dipole moments, can hydrogen bond and can also serve to accept acidic functionalities, e.g., the counter-ions of amine salts, in doing all these things releasing the free base forms of molecularly dissolved salts to diffuse through the adhesive and partition into the skin as free bases. In stark contrast, the '075 application teaches the use of hydrophobic polymers, most particularly acrylate polymers, used in conjunction with highly plasticizing drugs, that is, drugs that are liquid or near liquid[3] at room temperature. The '075 application does not teach the use of amine containing polymers to dissolve a drug nor does it teach the use of amine containing polymers to free up the free base forms of amine salts from the amine salts. Indeed, it directly and explicitly teaches against both these ideas.

8. In the case of acrylic acid, a rather small molecule, the addition of an amine group has a profound effect on polarity. It imparts a dipole moment of considerable strength and, as a result of the unpaired electrons on the nitrogen atom of the amine functionality, it affords strong

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[2] Physical chemists tend to see polarity strictly in terms of the dipole moments of molecules. This view is incomplete and unsatisfactory from a pharmaceutical view for, on the basis of this view, butyl chloride would be more polar that either ethanol or water, of itself a ridiculous supposition. Consequently, all biological and pharmaceutical scientists couch polarity in terms of the partitioning of a substance between an oil and water, most usually n-octanol and water. Highly water interactive molecules that concentrate in the water phase are then considered polar while hydrophobic molecules that concentrate in the oil phase are not. A dipole moment of average strength is not, of itself, sufficient to make a compound polar from the standpoint of partitioning and therefore from the standpoint of mass transfer across a lipophilic membrane such as the skin.

[3] The term, "near liquid," used here simply refers to nominally solid compounds that have melting points just above room temperature.

hydrogen bonding with the molecule, stronger in fact than the hydroxyl (-OH) group so often associated with the hydrogen bonding of organic molecules.[4] Thus, when amine monomers are polymerized, a large number of amine groups are added to the polymer backbone as pendant groups, which can then engage in strong hydrogen bonding as well as dipolar interactions. Clearly, this dramatically alters the solubilization (solubility) properties of these polymers, making them substantially hydrophilic. It is thus my opinion that in the case of acrylic acid, for example, the presentation of amino-group-containing monomers will have a profound effect on the charge and polarity of the formed polymer molecule and most particularly add a hydrogen bonding ability to the polymer molecule. This makes the polymer profoundly hydrophilic, particularly as compared with a hydrophobic polymer containing no amino-group functionalities as specified by the '075 application.

9. It is therefore also clear to me that Müller *et al.* does not suggest to anyone of ordinary skill in this art that they should produce a hydrophobic (non-hydrogen bonding, essentially electrically neutral) acrylic polymer, as is required, however, by the claims in the '075 application. It is also clear to me that they do not suggest any transdermal product including a highly plasticizing drug, since the only drug disclosed in Müller *et al.*, namely bopindolol hydrogen maleate, is a solid, and certainly not a highly plasticizing drug such as those set forth in the '075 application, nor is it a liquid at room temperature.

[4] Butanol is only partially miscible with water at room temperature while butyl amine is fully miscible, showing that a single $-NH_2$ group can draw more methyl and methylene groups into water than a single -OH group.

10. It is also clear to me that the idea of using a hydrophobic polymer, most particularly an acrylate polymer, in conjunction with a highly plasticizing drug is a novel and inventive idea beyond the skill of someone of ordinary skill in this art. This is so because highly plasticizing drugs lack crystallinity and thus tend to be highly soluble in many media. They therefore can be overly soluble in a polar acrylate matrix for their efficient delivery as a result of the fact that the polymer they are placed in is too interactive with them. Being too interactive lowers their activities at any given concentration, thereby reducing the abilities they have to partition into the skin. Hydrophobic polymers are <u>not</u> good solvents and thereby offer higher activities and better partitioning into the skin to all drugs more polar than they are (essentially all drugs).

I hereby declare that all the statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing therefrom.

Dated: 1/13/05

By Gordon L Flynn
DR. GORDON L. FLYNN

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